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Dear Professor Lederberg,

Thank you for your letter, and the enclosed class notes which I was very interested to see. I have sent to you under separate cover two more copies of my J.Hyg paper. I am very glad that you think it may be of some use. I should certainly be glad to receive any of your future reprints which you think might be comprehensible to me (I am no bacteriologist!)

This question of what exactly one means by the mutation rate is very confusing, and matters are not helped by the fact that the models in which one assumes that the population increases in synchronised generations seem to give different answers to those in which one assumes that N increases smoothly (the division cycles being supposed to have got quickly out of step). I have used the latter type of model.

This difference in approach probably explains some discrepancies between my formulae and yours. For instance, comparing your (1a) with my (9), it would appear that

your $\underline{a}$ = my $\underline{\lambda}$.

But comparing your (2) with my (5) (or rather its limiting form $\psi = a\lambda t$), it appears that

your $\underline{a}$ = my $(2\log_e 2)\underline{\lambda}$.

I think discrepancies like this are bound to arise when one tries to match up continuous models with discontinuous ones.

I worked in terms of λ largely for mathematical convenience. Whether one regards λ as being the most useful measure of the mutation rate depends, I think, on some assumption as to whereabouts on the division cycle a mutation takes place. (cf. § 3.5 on pp. 168-9 of my paper) Suppose we always define λ by equation (8) - a function of mutations, rather than mutants. If we are willing to accept the reasonableness of a continuous model, and if we also make my assumption (a) (p. 167) then the various formulae in my paper can be used, and the mutation rate per individual bacterial cycle is $\lambda \log_e 2$. If we use a continuous model, but make my assumption (b) (which I think is your assumption (b), too), then the mutation rate per cycle is $\lambda/2$, (cf. § 3.5), and the rate per preceding division is λ . But now we have the difficulty that the formulae relating to numbers of <u>mutants</u> are no longer correct (cf. top of p. 168).

All these difficulties are, I think, unavoidable, and probably not very important in comparison with other sources of uncertainty such as phenotypic delay.

With regard to methods of estimation based on the mean of a single distribution, I think they should be avoided whenever possible, as they do not appear to have any advantages over other methods such as that using the upper quartile. I agree that, on the average, Luria & Delbrück's method will over-estimate the mutation rate. It is also true, I think, that a single determination will over-estimate the true value considerably more often than not. (cf. Method 6, p. 178).

Yours sincerely,

Peter Armitage

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